Dynamic prediction of death in patients with tuberculous meningitis using time-updated Glasgow coma score and plasma sodium measurements

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Summary: We used time-updated Glasgow coma score and plasma sodium measurements, together with baseline patient characteristics, in a model to dynamically predict death in adults with tuberculous meningitis. Predictions can be made from any time point until day 30 of follow-up.

Abstract

Background: Pre-treatment predictors of death from tuberculous meningitis (TBM) are well-established, but whether outcome can be predicted more accurately after the start of treatment by updated clinical variables is unknown. Hence, we developed and validated models that dynamically predict mortality using time-updated Glasgow coma score (GCS) and plasma sodium measurements, together with patient baseline characteristics.

Methods: We included 1048 adults from four TBM studies conducted in southern Vietnam from 2004-2016. We used a landmarking approach to predict death within 120 days after treatment initiation using time-updated data during the first 30 days of treatment. Separate models were built for patients with and without human immunodeficiency virus (HIV) infection. We used the area under the receiver operating characteristic curve (AUC) to evaluate performance of the models at day 10, 20 and 30 of treatment to predict mortality by 60, 90 and 120 days. Our internal validation was corrected for over-optimism using bootstrap. We provide a web-based application that computes mortality risk within 120 days.

Results: Higher GCS indicated better prognosis in all patients. In HIV-infected patients, higher plasma sodium was uniformly associated with good prognosis, whereas in HIV-uninfected patients the association was heterogeneous over time. The bias-corrected AUC of the models ranged from 0.82-0.92 in HIV-uninfected, and 0.81-0.85 in HIV-infected individuals. The models outperformed the previously published baseline models.

Conclusions: Time-updated GCS and plasma sodium measurements improved predictions based solely on information obtained at diagnosis. Our models may be used in practice to define those with poor prognosis during treatment.

Keywords: Tuberculous meningitis; mortality; HIV; dynamic prediction

Introduction

Tuberculous meningitis (TBM) is now one of the commonest causes of life-threatening meningitis worldwide, a distinction driven by the continued ability of *Mycobacterium tuberculosis* to evade global control efforts, the strong link between human immunodeficiency virus (HIV) infection and TBM, and the success of vaccination programmes against other bacterial causes of meningitis [1]. Despite the best available anti-tuberculosis drug treatment, death occurs in around 20% of HIV-uninfected and 40% of HIV-infected patients [2,3]. Survivors are often left with irreversible neurological sequelae, which severely affects their quality of life [4].

The pre-treatment predictors of poor outcome from TBM are well-studied. The British Medical Research Council (MRC) score to grade TBM severity has been used since 1948. Although it was defined empirically, rather than by statistical derivation, it has repeatedly been shown to be a good pre-treatment predictor of death from TBM [5–8]. It combines information on the patient's conscious state, assessed since 1974 by the Glasgow Coma Score (GCS) [5], and focal neurological deficits. More recently, statistical modelling of data from large cohorts of patients with TBM have revealed other strong predictors of death, including HIV infection, older age, multi-drug resistance, and low numbers of cerebrospinal fluid (CSF) white cells [6,8–10]. Indeed, we recently built and validated models for 9 month-mortality using a pooled database from five randomized controlled trials (RCT) and one observational study on TBM [8]. The models were based on several pre-treatment clinical variables and better predicted subsequent death than the MRC grade alone.

TBM requires 9-12 months of anti-tuberculosis drug treatment, during which complications from both the disease and the drugs can occur [2]. These complications change the likelihood of a poor outcome from TBM, but are not captured by current prognostic models based on pre-treatment variables alone. Currently, there are no published models that take into account changing clinical variables after the start

of TBM treatment. Therefore, our aim was to develop and validate dynamic prediction models that incorporate baseline patient characteristics, as well as follow-up measurements (time-updated values) of GCS and plasma sodium. Our models were constructed using a large sample of 1048 Vietnamese adults with TBM. During the first 30 days of anti-tuberculosis treatment, we used updated information to predict mortality within the first 120 days. This time range of 30 days was selected based on our clinical experience that the first 30 days are critical to outcome. Most patients are hospitalised during this period and repeated measures of GCS and plasma sodium are usually available. We compared the predictive performance of these dynamic models to the previously published baseline models [8].

Methods

Study population

We used data from three RCTs [3,11,12] and one observational study [13] on TBM which provided longitudinal information of GCS and plasma sodium during follow-up. The studies were conducted between 2004 and 2016 at Pham Ngoc Thach Hospital and the Hospital for Tropical Diseases, which are two tertiary referral hospitals in southern Vietnam. Patients were included in the studies if they were clinically diagnosed with TBM, defined as having more than 5 days of meningitis symptoms and CSF abnormalities. TBM diagnosis was categorised in all study participants as definite, probable, and possible. These diagnostic categories were defined by study-specific criteria in all patients enrolled before 2010 and by published consensus criteria from 2010 onwards [14]. A summary of the studies and their inclusion criteria is provided in supplementary Table S1. The laboratory investigations and anti-tuberculosis and adjunctive treatment are described in detail elsewhere [8]. The management of low or high plasma sodium was not standardised in any of the studies, but left to the individual practice of the attending physician. Study participants were excluded if no information on GCS or plasma sodium was available, if any of the baseline risk factors were missing, if an alternative diagnosis to TBM was

confirmed, or if standard first-line anti-tuberculosis drug treatment was not given. All studies were approved by the Oxford Tropical Research Ethics Committee and the Hospital for Tropical Diseases and Pham Ngoc Thach Hospital Ethics Committees.

Primary outcome

The primary outcome for this study was defined as overall mortality during 120 days from the start of anti-tuberculosis treatment. Follow-up was restricted to 120 days because deaths occurring within this period are much more likely to be attributable to TBM rather than an alternative cause. Since anti-tuberculosis treatment usually started immediately following TBM diagnosis, time since TBM diagnosis and time since the initiation of anti-tuberculosis treatment can be seen to refer to the same time point in our analysis.

Predictors

As in our previous prognostic modelling study [8], we constructed separate prediction models for HIV-uninfected and HIV-infected patients. Our new models included both baseline patient characteristics and the longitudinal measurements of GCS and plasma sodium. We chose GCS and plasma sodium because both have been shown to be good pre-treatment predictors of death from TBM and both are monitored regularly in almost all settings. In the first 30 days of follow-up, most patients had daily GCS measurements in one trial [3] and weekly in the other studies. Plasma sodium was mostly measured daily for patients in one trial [12] and weekly in the other studies. We did not include other biomarkers such as CSF protein or ratio of CSF to blood glucose because on average we only had two measurements per patient in the first 30 days, precluding the development of a robust model.

We included the baseline characteristics that were identified as predictors of death within 9 months in our previous publication [8]. Specifically, in the HIV-uninfected population, these were age, history of previous TB treatment, MRC grade, focal neurological signs, and CSF lymphocyte count. In the HIV-

infected population, these were weight, MRC grade, CSF lymphocyte count, study cohort, and peripheral blood CD4 cell count. Baseline laboratory values were defined as values recorded closest to enrolment (up to ±7 days from enrolment) [8]. Compared to the previous analysis, we excluded patients enrolled in two studies [15,16] because their GCS and plasma sodium after the start of anti-tuberculosis treatment were not available. However, we retained the study cohort variable in the model for HIV-infected patients to account for improvements in treatment and patient supportive care over the last 15 years in Vietnam. The most significant of these was the nation-wide scale-up of free HIV antiretroviral therapy since 2005 [17]. We included sodium in the model for both populations, and used it as a time-updated instead of as a baseline variable.

Statistical analysis

The details of the statistical analysis are given in the Supplementary appendix S1. In brief, we used a mixed model landmark approach [18,19]. We constructed a prediction model at a range of landmark time points: from day 0 to day 30 after diagnosis. For each landmark time, we created a data set including all patients who were still alive up to that landmark time point. For GCS, we used the last available measured value up till 10 days prior to the landmark time. With plasma sodium, we used the fitted value at the landmark time obtained from a linear mixed-effects model as explained in the appendix. To obtain predictions over a range of different time points using a single model, we implemented the "landmarking super model" approach [20]. Specifically, we combined the 31 landmark data sets, one for each day since initiation of anti-tuberculosis treatment until day 30. The stacked data was analysed using a Cox proportional hazards model with landmark time included as a stratification factor. We allowed for a non-linear relation between sodium and mortality that can vary over time. Other predictors were included linearly. We also explored a number of extra analyses and an alternative modelling approach, which are described in the Supplementary appendix S1.

We assessed the discrimination and calibration ability of the models based on the area under the receiver operating characteristic curve (AUC), the Brier score (i.e. the prediction error with a square loss function) [18], and the calibration plot [21] . A higher AUC value and a lower Brier score indicate better performance. The evaluation was carried out at day 10, 20 and 30 for mortality until day 60, 90 and 120 after diagnosis. We also calculated the AUC and Brier score of the published baseline model [8] at the same prediction times using our landmark data sets. We used bootstrap internal validation to correct for the over-optimism in the predictive performance [22]. The final models have been implemented in a web-based calculator to facilitate their application in clinical practice. All analyses were conducted using R software, version 3.5.0 [23].

Results

Baseline characteristics of study participants

In total, there were 1248 patients in the four studies, of which 1068 were included in the analysis. The reasons for excluding the other 180 patients were: confirmed other diagnosis (n = 16), first-line anti-tuberculosis drugs not received (n = 3), missing information on either of the two markers (n = 7), missing values for at least one of the baseline patient characteristics (n = 154). Baseline characteristics of the included patients are given in Table 1. 550 (51%) were HIV-uninfected, and 518 (49%) were HIV-infected. The median age was 34 years (interquartile range (IQR): 27-44). Out of 1068 patients, 395 (37%) were MRC grade I, 459 (43%) were MRC grade II, and 214 (20%) were MRC grade III. The number of definite TBM (microbiologically confirmed TBM) cases was 636/1068 (60%). In HIV-infected subjects, the median peripheral blood CD4 count was 40 cells/µL (IQR: 15 - 101). Compared to the HIV-uninfected, HIV-infected patients were younger (median age 31 years vs. 41 years), were admitted to the hospital in more severe condition (MRC Grade III 24.9% vs. 15.5%), and more likely to be classified as having definite TBM (70% vs. 50%).

Figure S1 displays the Kaplan-Meier estimate of the overall survival by HIV status. During the 120 days of follow-up, the number of deaths was 76/550 (14%) in the HIV-uninfected group, and 202/518 (39%) in the HIV-infected group.

Longitudinal profile of GCS and plasma sodium

During the first 30 days of treatment, HIV-uninfected patients had a mean of 21 (median (IQR): 27 (7-31)) GCS assessments and HIV-uninfected patients had a mean of 14 (median (IQR): 5 (5-29)) assessments. The mean numbers of plasma sodium measurements was 6 (median (IQR): 5 (4-7)) and 4 (median (IQR): 5(3-5)) in HIV-uninfected and HIV-infected patients, respectively. Figure 1 depicts the individual trajectories of the two markers as well as their median value and quartiles during the first 30 days. All survivors, independent of HIV status, tended to have higher GCS than those who died. Plasma sodium values were also higher in HIV-infected survivors, with a less clear relationship between sodium and survival in HIV-uninfected patients.

Parameter estimates

Table 2 gives parameter estimates of the dynamic landmark supermodels. Regarding GCS, a higher value indicated lower mortality with a hazard ratio of 0.76 (95% confidence interval (CI): 0.71-0.81) and 0.85 (95% CI: 0.81- 0.91) in HIV-uninfected and HIV-infected patients respectively. Figure 2 displays the hazard ratio for sodium at day 0, 10 and 30. Sodium concentrations of 135 mmol/L were taken as the reference. As can be seen, the association between plasma sodium and mortality differed by HIV status. In HIV-uninfected patients, it was heterogeneous over time. Higher sodium concentrations were associated with worse prognosis from baseline until day 10 of treatment. However, by day 30, higher sodium concentrations were associated with increased survival. In HIV-infected patients, higher sodium concentrations uniformly associated with better prognosis across all prediction time points.

Compared with the published baseline model [8], the strength of the association between MRC grade and mortality was attenuated with the inclusion of time-updated GCS. This is not surprising as GCS is strongly correlated with MRC grade. The strength of the association for the other baseline covariates was similar between the dynamic models and the baseline models, except for history of previous TB treatment in the model for HIV-uninfected patients. The hazard ratio for this predictor was 0.57 indicating a beneficial effect which contradicted with that in the baseline model (HR = 1.57, CI 1.09 - 2.26). However, it was not statistically significant at 0.05 level (p-value = 0.27, CI 0.21-1.54).

Predictive performance

All the considered alternative analyses (Supplementary appendix S1) did not improve the predictive performance of the models.

The dynamic prognostic model showed good discrimination between survivors and deaths, with corrected AUC ranging from 0.82-0.92 in HIV-uninfected, and from 0.81-0.85 in HIV-uninfected patients across the chosen landmark and prediction times (Table 3). The dynamic models clearly improved over the published baseline models [8], which had AUCs from 0.75-0.81 in HIV-uninfected and from 0.71-0.76 in HIV-infected subjects. In terms of calibration, Figure S2 shows good agreement between the predicted risks and the observed risks for all three chosen landmark time points. Overall performance, as measured by the Brier score, was also improved in the dynamic models compared to the baseline models (Table S2).

Model display and illustration

We implemented the models in a user-friendly web-based calculator, which is available at: https://thaole.shinyapps.io/DynamicTBMApp/. The web calculator allows the user to make predictions of mortality within 120 days after the initiation of TB treatment from any of the first 30 days. As in the baseline model's web calculator for HIV-infected patients (https://thaole.shinyapps.io/TBMApp/), we chose the intensified trial [3] as cohort variable because it is the most recent cohort.

In Figure 3, we illustrate the use of the model to dynamically predict mortality until day 120 for a 39 years old HIV-uninfected patient without previous TB, having MRC grade III, no focal neurological signs at enrolment and with CSF lymphocyte count at baseline of 73.5 cells/µL (patient A). A similar illustration for an HIV-infected patient (patient B) is in Supplementary Figure S3. Baseline characteristics of the two patients are documented in Supplementary Table S3. As can be seen, the predicted survival probability is updated as new information on GCS and plasma sodium becomes available. Of note, the risk predictions can vary substantially over the landmark days, indicating the importance of updating prediction using the most recent information.

Discussion

Using most recent information on disease state is important for monitoring patients, tailoring treatment and improving disease outcomes. We developed and validated a dynamic prediction model for death in TBM patients with and without HIV coinfection. The models used time-updated information on Glasgow coma score and plasma sodium as well as baseline patient characteristics. Indeed, our model provided better predictive performance than the model that only used baseline characteristics [8].

Our model confirmed that GCS is a strong predictor of outcome in both populations. Regarding plasma sodium, hyponatraemia is a common complication of TBM, usually caused by cerebral salt wasting or the syndrome of inappropriate anti-diuretic hormone[7]. Its impact upon survival has not been well-studied, although low sodium concentrations can cause reduced consciousness and exacerbate raised intracranial pressure. Mostly, higher sodium concentrations during treatment indicated better outcome. While this association was uniformly observed over the first 30 days of treatment in HIV-infected patients, in HIV-uninfected patients higher concentration predicted worse outcomes in the first 10 days of treatment, and switched to predicting better outcomes thereafter (Figure 2). This is an intriguing finding which is not easily explained. Possible explanation may be the contribution of

neurogenic diabetes insipidus, which occurs in severe disease affecting the hypothalamic-pituitary access [24], and can cause harmful hypernatraemia. It is unclear why HIV-infection may drive these differences and the findings increase the importance of better understanding and managing disorders of sodium homeostasis associated with TBM.

In our database, there are seven HIV-uninfected patients and eight HIV-infected patients with at least one measurement of plasma sodium higher than 145 mmol/L (hypernatraemia) in the first 30 days. Of those, seven patients died (four in HIV-uninfected and three in HIV-infected patients). All of these deaths happened very early, within the first 25 days since the start of anti-tuberculosis treatment. Due to the low number of hypernatraemia cases and the timing of the events, the impact of high sodium values on mortality was not captured thoroughly in our model, especially at later landmark times.

Our study has several limitations. First, we only considered GCS and plasma sodium as time-updated markers. Including other markers could potentially improve the model predictive performance. In order to include them in future studies, they should be collected more frequently over time. Second, the models were developed and validated using data solely from two recruiting centres in the South of Vietnam. This restriction may affect the generalisability of the models. Thus, the models require validation in different patient populations.

In conclusion, our dynamic prediction models allowed us to predict 120-day mortality from TBM using time-updated data from the first 30 days of treatment. The models were carefully constructed and validated internally based on a large data set of 1048 patients. To the best of our knowledge, they are the first published dynamic prediction models for TBM. We hope that they will be validated in other patient populations and prove useful in practice by providing clinicians and patients better information and facilitate decision making regarding treatment and patient management.

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Conflict of interest: none to declare

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Table 1: Baseline characteristics of patients with tuberculous meningitis included in the pooled database, overall and by human immunodeficiency virus status

		All patients (N=1068)		HIV-uninfected (N=550)		HIV-infected (N=518)
Characteristic	n[a]	Summary statistic	n[a]	Summary statistic	n[a]	Summary statistic
Cohort*	1068		550		518	
- Intensified treatment trial		689 (64.5%)		431 (78.4%)		258 (49.8%)
- Aspirin trial		119 (11.1%)		119 (21.6%)		0(0%)
- TBM HIV cohort		44 (4.1%)		0 (0%)		44 (8.5%)
- ART timing trial		216 (20.2%)		0 (0%)		216 (41.7%)
Age (yrs), median (IQR)	1067	34(27,44)	550	41(29,53)	517	31(27,36)
Weight (kg), median (IQR)	1068	48(43,54)	550	50(45,55)	518	46(41,51)
Previous tuberculosis treatment	1062	162 (15.3%)	550	50 (9.1%)	512	112 (21.9%)
MRC grade[b]	1068		550		518	
- Grade I		395 (37%)		208 (37.8%)		187 (36.1%)
- Grade II		459 (43%)		257 (46.7%)		202 (39%)

- Grade III		214 (20%)		85 (15.5%)		129 (24.9%)
Focal neurological signs present	1056	528 (50%)	550	321 (58.4%)	506	207 (40.9%)
CSF lymphocyte count (cells/μL), median (IQR)	1068	94.5(35,208.7)	550	104.8(42,213.1)	518	80.7(25.2,204.8)
Microbiologically confirmed/definite TBM	1068	636 (59.6%)	550	274 (49.8%)	518	362 (69.9%)
Peripheral blood CD4 count (cells/μL), median (IQR)	-	-	-	-	518	40(15,101)

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IQR, interquartile range; MRC, Medical Research Council; TBM, tuberculous meningitis.

[a]Number of subjects with non-missing data for the respective characteristic. Note: the number of individuals with measured values can be lower than the maximum (550 resp. 518), but these risk factors were not part of the model for that HIV subpopulation.

[b]Grade I: Glasgow Coma score (GCS) 15 with no focal neurological signs; Grade II: GCS 11–14, or 15 with focal neurological signs; Grade III: GCS ≤10.

* Included studies are described in the supplementary Table S1.

Table 2: Parameter estimates (with 95% confidence intervals) from landmark supermodel by HIV status

	HIV-uninfected TBM population		HIV-Infected TBM population	
Variable	**HR**	**95% CI**	**HR**	**95% CI**
Age (per +10y)	1.51	(1.34; 1.69)	-	-
Weight (per +10kg)	-	-	0.59	(0.47; 0.75)
MRC grade[a]				
- Grade I	1	-	1	-
- Grade II	1.02	(0.37; 2.83)	1.48	(0.99; 2.21)
- Grade III	1.48	(0.43; 5.05)	1.37	(0.77; 2.45)
Previous tuberculosis treatment	0.57	(0.21; 1.54)	-	-
Focal neurological signs present	1.45	(0.60; 3.54)	-	-
CSF lymphocyte count[b], cells/µL	0.78	(0.68; 0.89)	0.99	(0.91; 1.08)
Cohort	-	-		
- Intensified trial	-	-	1	
- TBM HIV cohort	-	-	2.55	(1.62; 4.02)
- ART timing trial	-	-	1.55	(1.10; 2.18)
Peripheral blood CD4 count[b], cells/µL	-	-	0.92	(0.83; 1.01)
Time-updated Glasgow coma score	0.76	(0.71; 0.81)	0.85	(0.81; 0.91)
Time-updated plasma sodium,	-	-	-	-

mmol/L[c]				
- Plasma sodium 125 vs 135 mmol/L	-	-	-	-
- Landmark time = day 0 (baseline)	0.45	(0.29; 0.71)	1.67	(0.64; 4.36)
- Landmark time = day 10	0.98	(0.54; 1.77)	3.21	(2.11; 4.87)
- Landmark time = day 30	2.93	(1.63; 5.25)	3.10	(1.98; 4.83)
- Plasma sodium 140 vs 135 mmol/L	-	-	-	-
- Landmark time = day 0 (baseline)	2.37	(1.53; 3.67)	0.88	(0.31; 2.52)
- Landmark time = day 10	1.09	(0.65; 1.82)	0.50	(0.28; 0.88)
- Landmark time = day 30	0.27	(0.09; 0.87)	0.32	(0.16; 0.61)

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; HR, hazard ratio; MRC, Medical Research Council; TBM, tuberculous meningitis.

[a] grade I: Glasgow Coma score (GCS) 15 with no focal neurological signs; grade II: GCS 11–14, or 15 with focal neurological signs; grade III: GCS ≤10

[b]HR per 2-fold increase.

[c]The association of sodium levels and mortality was allowed to vary in a flexible manner. The p-value for the interaction between sodium and time was <0.001 and 0.18 respectively for the HIV-uninfected and HIV-infected subgroups. To simplify interpretation, we give HRs for two derived sodium contrasts at three different landmark time points.

Table 3 Discrimination of the dynamic model by human immunodeficiency virus (HIV) population measured by area under the curve (AUC). The prediction was carried out at day 10, 20 and 30 for mortality until day 60, 90 and 120 after diagnosis.

			Bias-corrected AUC	
Landmark time	**Prediction time[a]**	**Model**	**HIV-uninfected population**	**HIV-infected population**
10	60	Dynamic model	0.819	0.829
		Baseline model	0.769	0.762
	90	Dynamic model	0.834	0.825
		Baseline model	0.787	0.753
	120	Dynamic model	0.839	0.814
		Baseline model	0.810	0.745
20	60	Dynamic model	0.866	0.832
		Baseline model	0.775	0.737
	90	Dynamic model	0.869	0.842
		Baseline model	0.795	0.728
	120	Dynamic model	0.866	0.825
		Baseline model	0.818	0.721
30	60	Dynamic model	0.919	0.843
		Baseline model	0.748	0.725
	90	Dynamic model	0.890	0.845

	Baseline model	0.780	0.716
120	Dynamic model	0.890	0.816
	Baseline model	0.811	0.709

[a]Prediction time refers to days after the initiation of anti-TB treatment.

Figure captions:

Figure 1: Subject specific profiles for Glasgow coma score (GCS) and plasma sodium over the first 30 days, stratified by observed survival status within 120 days. The dark blue line represents the median value per day, the blue area represents the interquartile range. Plasma sodium of HIV-uninfected patients is plotted as (log2(plasma sodium - 100) with the original value as label.

Figure 2: Hazard ratio for plasma sodium at three landmark times: day 0, day 10 and day 30 after the start of TB treatment. A sodium value of 135 mmol/L was taken as the reference. The shaded areas represent the 95% confidence intervals.

Figure 3: Dynamic predictions of survival for patient A at four different days after the start of TB treatment. For each day, the left panels display the observed values of GCS and plasma sodium over time, the blue line represents the fitted value for sodium. The right panels represent the estimated survival probability in red with 95% confidence intervals in grey.

Figure 1

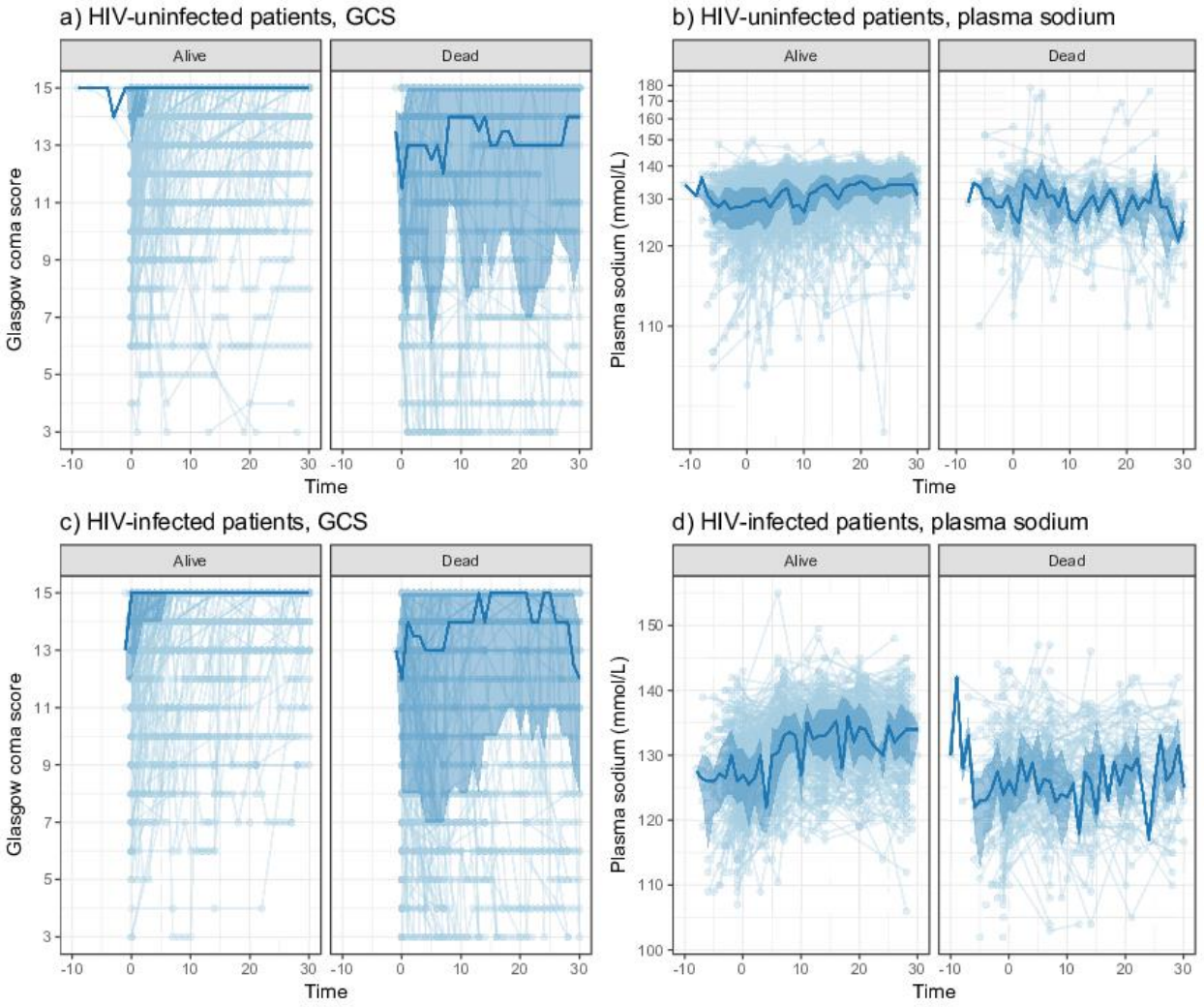

Figure 2

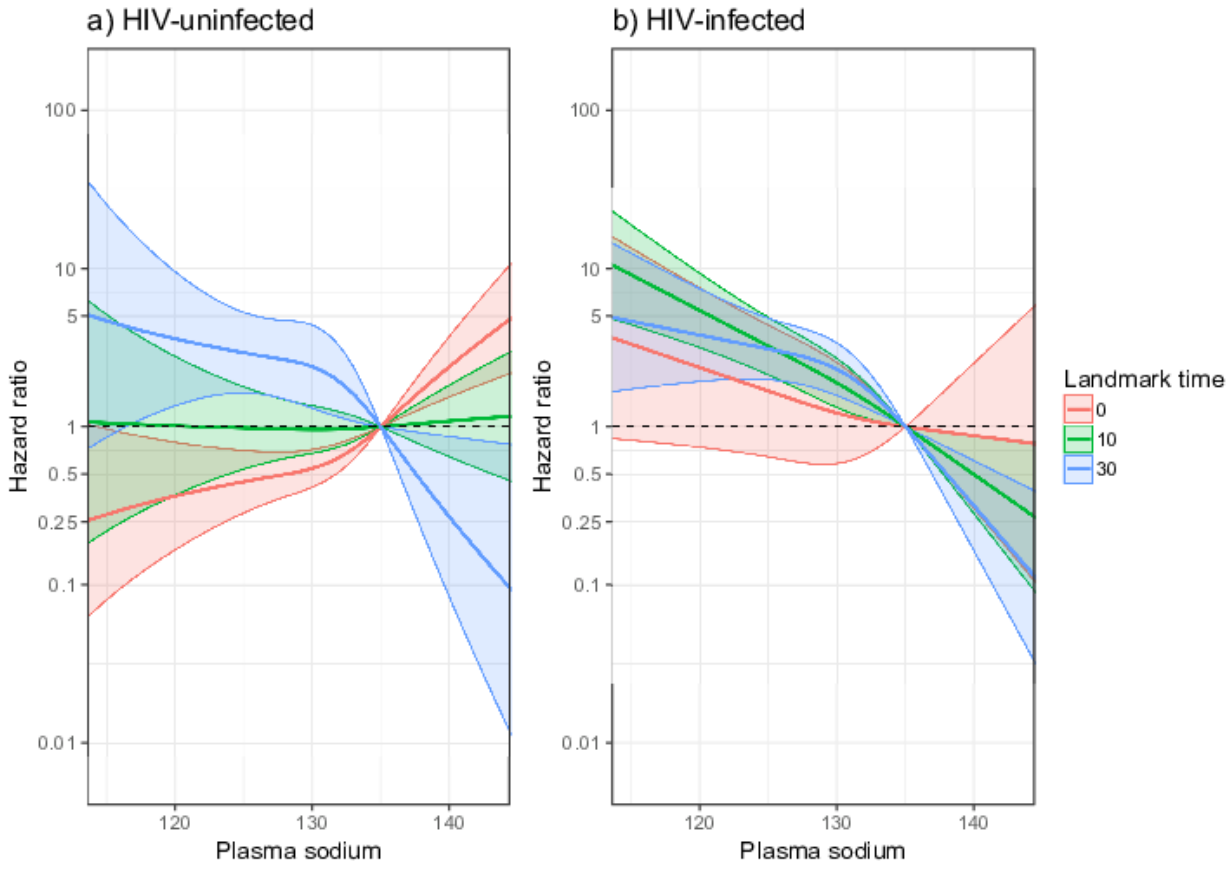

Figure 3